CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20098/S009

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

JUN 2 5 1998

Clinical Pharmacology and Biopharmaceutics Review

NDA: 20-098	**Supplement No.**: S-009
Name: Mivacron® (Mivacurium chloride) for injection	
Sponsor: Glaxo Wellcome Inc., Five Moore Dr.,	Research Triangle Park, NC
Submission Type: Labeling Supplement	**Submission Date**: May 12, 1997
Reviewer: Suresh Doddapaneni, Ph.D.	

Addendum to the Primary Review

Background:

Supplement S-009 to NDA 20-098 was approved on May 19, 1998. Glaxo Wellcome Inc., used data submitted in supplement S-009 to propose several changes to the original package insert. However, after reviewing the data submitted in this supplement, the language and content of the pharmacokinetics section of the package insert was changed by the Agency from what was proposed by the sponsor (see Clinical Pharmacology and Biopharmaceutics review dated April 24, 1998). Although most changes suggested by the Agency were agreeable to Glaxo Wellcome Inc., a request was made by the company to reinsert the following paragraph in the introduction of the pharmacokinetics section of the package insert;

> The two more potent isomers, *cis-trans* (36% of the mixture) and *trans-trans* (57% of the mixture), have very high plasma clearances (CL) that exceed cardiac output, reflecting the extensive metabolism by plasma cholinesterase (Table 3). The volume of distribution is relatively small, reflecting limited tissue distribution secondary to the polarity and large molecular weight of mivacurium. The combination of high metabolic clearance and low distribution volume results in the short elimination half-life of approximately 2 minutes for the two active isomers. The short elimination half-lives and high metabolic clearances of the active isomers are consistent with the short duration of action of MIVACRON.

The rationale provided for the request was;
"In order for the pharmacokinetic information to be used appropriately, the information (cis-trans (36% of the mixture) and trans-trans (57% of the mixture)) is needed in the package insert. Additionally, we feel that without this information, there was not a good transition into the final sentence of that section and that there is no reference to Table 3".

Discussion:

It should be pointed out that essentially same information exists in the package insert at a different location and that this information was not deleted. The paragraph being referred to by the company was deleted/modified by the Agency to

streamline the information according to the ADME format and to avoid redundancy. Specifically, sentences 1 and 3 of the above paragraph still exist in the Elimination subsection of the Pharmacokinetics section of the package insert (page 8). A modification of the sentence 2 of the above paragraph can be found in the Distribution subsection of the Pharmacokinetics section of the package insert (page 7).

Recommendation

The following information should be conveyed to the company;

The information contained in the paragraph in question has not been deleted from the package insert. Specifically, sentences 1 and 3 of the paragraph still exist in the Elimination subsection of the Pharmacokinetics section of the package insert (page 8). A modification of sentence 2 of the paragraph can be found in the Distribution subsection of the Pharmacokinetics section of the package insert (page 7). Reference to Table 3 appears at both locations. These changes were made to streamline the information and to avoid redundancy.

6/25/98

Suresh Doddapaneni, Ph.D.
Pharmacokineticist
DPEII/OCPB

RD initialed by Ramana Uppoor, Ph.D.
FT initialed by Ramana Uppoor, Ph.D. 06/25/98
CC:
NDA 20-098, HFD-170 (Division files, Nolan), HFD-850 (Lesko), HFD-870 (Doddapaneni, Mei-Ling Chen, Uppoor), Central Document Room (Barbara Murphy).

APR 2 4 1998

Clinical Pharmacology and Biopharmaceutics Review

NDA: 20-098
Name: Mivacron® (Mivacurium chloride) for injection
Sponsor: Glaxo Wellcome Inc., Five moore Dr., PO Box 13398, Research Triangle Park, North Carolina 27709
Submission Type: Labeling Supplement **Submission Date**: May 12, 1997
Reviewer: Suresh Doddapaneni, Ph.D.

SYNOPSIS

Mivacron® (Mivacurium chloride) for injection, subject of NDA 20-098, was approved for marketing in January of 1992. Mivacurium chloride is comprised of three stereoisomers, *cis-trans*, *trans-trans*, and *cis-cis* isomers. *Cis-trans* and *trans-trans* comprise about 92-96% of mivacurium and are equipotent. *Cis-cis* isomer comprising only 4-8% of mivacurium is not considered to contribute greatly to the neuromuscular blocking action of mivacurium. At the time of approval, the sponsor agreed to conduct the following Phase IV studies; *in vitro* hydrolysis rates of the isomers, mass balance, long term infusions, and in the elderly, hepatic failure, and renal failure patients. This submission consists of final study reports for the above mentioned studies and proposed labeling changes for Mivacron® arising out of these studies.

RECOMMENDATION

The supplement SLR-009 to NDA 20-098 submitted on May 12, 1997 is acceptable from the viewpoint of the Office of Clinical Pharmacology and Biopharmaceutics. However, the sponsor should be sent the revised pharmacokinetic section of the package insert presented in Appendix II.

4/24/98

Suresh Doddapaneni, Ph.D.
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RD initialed by John Hunt on 4/23/98
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NDA 20-098, HFD-170 (Division files, Nolan), HFD-850 (Lesko), HFD-870 (Doddapaneni, Mei-Ling Chen, Hunt), Central Document Room (Barbara Murphy).

1.0. INTRODUCTION

Mivacron® (Mivacurium chloride) for injection, subject of NDA 20-098, was approved for marketing in January of 1992. Mivacurium chloride is a non-depolarizing neuromuscular blocking agent with a short duration of action. Mivacurium solution consists of a mixture of three isomers (composition specifications are given in parenthesis): *cis-trans* (34.1-39.6%), *trans-trans* (52.1-62.1%), and *cis-cis* (3.8-8.2%). The *cis-trans* and *trans-trans* isomers are equipotent and account for almost all of the neuromuscular blocking action. *Cis-cis* isomer is one-tenth as potent compared to the *cis-trans* and *trans-trans* isomers. Because, it's potency is relatively low and because it comprises only a minor component of mivacurium's composition, *cis-cis* isomer is not considered to contribute greatly to the neuromuscular blocking action of mivacurium. Mivacurium undergoes hydrolysis by plasma cholinesterase (pChE) to generate a quarternary alcohol metabolite (141U86) and a monoester metabolite (879U84) which are excreted in the urine and bile. A schematic of the metabolic pathway is shown in figure 1. Animal studies indicate that these metabolites are not pharmacologically active.

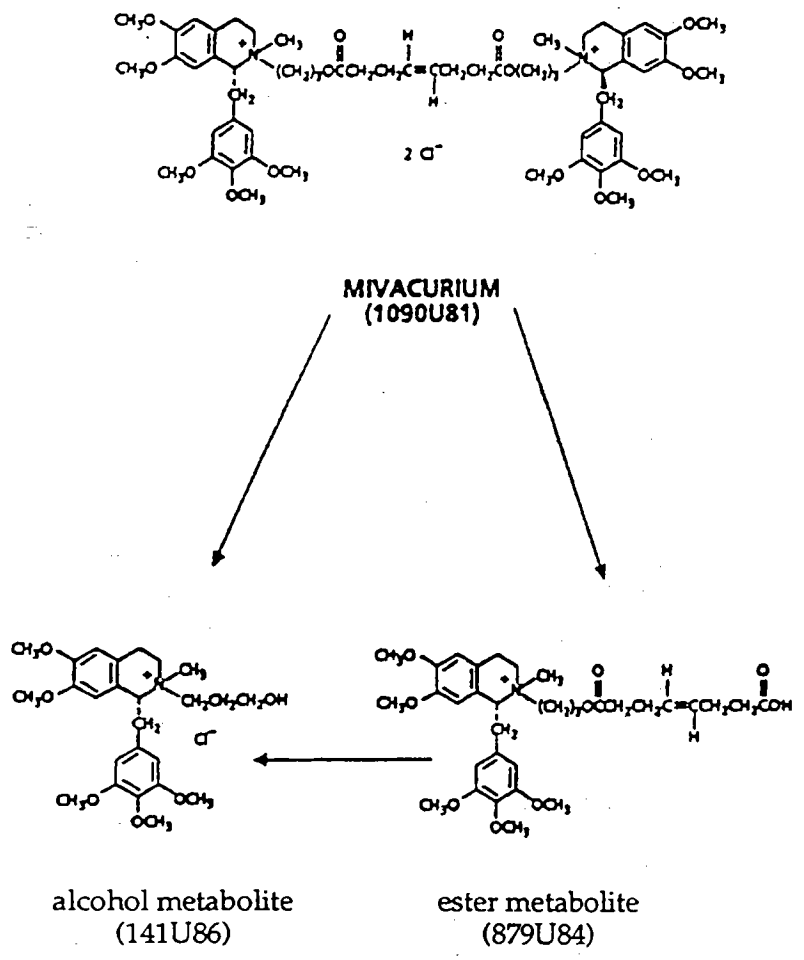

Figure 1. A schematic of the metabolic pathway of mivacurium.

Until recently the values of the pharmacokinetic parameters of the two active isomers have been estimated from the total mivacurium concentrations observed. These estimates were obtained by subtracting the longer half-life, less potent *cis-cis* mivacurium concentrations after back extrapolation of the terminal phase. This technique provides data for the *combined cis-trans* and *trans-trans* concentrations and is wholly dependent on the quality of the terminal phase (*cis-cis* concentrations). At the time of NDA approval, the sponsor agreed to conduct the following studies as Phase IV commitments;

"1. The pharmacokinetics and pharmacodynamics of mivacurium will be studied in patients receiving long-term infusions of mivacurium. Specifically, the steady-state plasma concentrations of the individual isomers and metabolites of mivacurium will be measured. In addition, the recovery profile upon termination of mivacurium will be determined.

2. Pharmacokinetic and pharmacodynamic studies will be performed in healthy patients and in patients with renal and hepatic dysfunction. The elimination pathways of the *cis-cis* isomer will be evaluated as part of these studies.

3. *In vitro* esterase hydrolysis studies will be performed on plasma collected from a variety of individuals."

This new submission consists of final study reports for the above mentioned studies and proposed labeling changes for Mivacron® arising out of these studies. Seven pharmacokinetic studies (either full pharmacokinetic studies or efficacy studies with a pharmacokinetic component) and one full efficacy study have been submitted in the current supplement. The seven pharmacokinetic studies are; study 8 (hepatic failure patients), study 11 (renal failure patients), study 12 (mass balance), study 14 & 33 (elderly patients), study 29 (healthy surgical patients), and report TBZZ/93/0062 (*in vitro* hydrolysis rates of mivacurium isomers). The full efficacy study (study 10) was conducted in renal failure patients. Evaluation of efficacy variables (for e.g., onset and depth of neuromuscular block and recovery from the neuromuscular block) in studies where both pharmacokinetics and pharmacodynamics were evaluated is deferred to the reviewing medical officer.

2.0. METABOLISM

2.1. *IN VITRO* ESTERASE HYDROLYSIS

Data on *in vitro* esterase hydrolysis of mivacurium was submitted to the Agency on March 1, 1994 (**Report TBZZ/93/0062**). However, this data was found to be deficient by the reviewing pharmacokineticist on the following two aspects; (1) Only an internal report was cited *in lieu* of submitting full analytical method validation (2) The composition of mivacurium used in the *in vitro* study was comprised of 45.9% of *trans-trans*, 40.6% of *cis-trans*, and 9.5% of *cis-cis* isomers (combined *trans-trans* and *cis-trans* amount of 86.5 is below the NDA content specification of %). The reviewer recommended that if the sponsor could submit standard curves and representative chromatograms and provide a rationale for the use of a sub-standard

drug product, the results of this study could be incorporated into the metabolism section of the label.

The sponsor in this new submission submitted the results of the standard curves and represantative chromatograms showing discrimination of the three isomers. The submitted analytical data appears to be satisfactory. The sponsor chose the batch with highest *cis-cis* isomer concentration (%) as high initial concentrations were needed to allow for adequate characterization of the concentrations for these isomers as a function of time with the supposition that the *in vitro* disappearance rates determined for the isomers would not be affected by the relative differences in the isomer content of the drug product. The rationale provided by the sponsor appears to be reasonable.

Results submitted in this report showed that the pharmacologically active *trans-trans* and *cis-trans* isomers were rapidly hydrolyzed by plasma cholinesterase with mean ± S.D. *in vitro* half-lives of 1.3 ± 0.3, and 0.8 ± 0.2 minutes, respectively. The relatively inactive *cis-cis* isomer disappeared much more slowly with an *in vitro* half-life of 275 ± 130 minutes. No gender differences were seen in the rates of hydrolysis of the stereoisomers (plasma was obtained from five male and five female volunteers). The sponsor compared this *in vitro* data with *in vivo* elimination half-lives of the stereoisomers of mivacurium in healthy surgical patients (report study 29). Although the *in vitro* and *in vivo* half-lives determined for the *trans-trans* and *cis-trans* isomers are similar, the *in vitro* half-life of the *cis-cis* isomer is longer than *in vivo* (275 minutes versus 53 minutes) suggesting that another route of elimination, other than ester hydrolysis, is important for the *cis-cis* isomer *in vivo*.

Labeling Comments:

The sponsor's following labeling statements on lines 195-202 of the package insert arising out of report TBZZ/93/0062 and study 29 are acceptable (note: the *in vivo* results mentioned in these statements come from study 29 which is discussed in section 2.3 of this review); "The mean ± S.D. *in vitro* $t_{1/2}$ values of the *trans-trans* and the *cis-trans* isomers were 1.3 ± 0.3 and 0.8 ± 0.2 minutes, respectively, in human plasma from healthy male (n=5) and female (n=5) volunteers. The mean *in vivo* $t_{1/2}$ values for the more potent *trans-trans* and *cis-trans* isomers in healthy surgical patients (Table 3) were similar to those found *in vitro*, suggesting that hydrolysis by plasma cholinesterase is the predominant elimination pathway for these isomers. The mean ± S.D. *in vitro* $t_{1/2}$ of the less potent *cis-cis* isomer was 276 ± 130 minutes, while the mean ± S.D. *in vivo* $t_{1/2}$ for the *cis-cis* isomer in healthy surgical patients was 53 ± 20 minutes. These data suggest that *in vivo*, pathways other than hydrolysis by plasma cholinesterase contribute to the elimination of the *cis-cis* isomer."

2.2. MASS BALANCE

This was an open label study with six (6) male patients undergoing elective extraction of wisdom teeth under nitrous oxide/oxygen/isoflurane anesthesia after induction with thiopentone (**Study 12**). The subjects received a single dose of 0.15 mg/kg ^{14}C-labeled mivacurium administered by i.v. bolus injection.

^{14}C Recovery in urine, feces, and breath:

The mean total percentage recovery of ^{14}C in urine and feces was 101% of the ^{14}C dose administered (approximately 40% of the dose in the urine and 60% in the feces). Urinary excretion of ^{14}C was complete by 24 hours. However, the recovery of ^{14}C in feces continued up to 168 hours. Since, all the patients received morphine for pre-medication and some of the patients also received opioids for post-operative analgesia, the prolonged recovery of ^{14}C in the feces when the recovery was complete within 24 hours in the urine may have been caused by the constipating effects of the opioids. No ^{14}C was excreted as $^{14}CO_2$ during the course of the anesthetic.

Urinary excretion of mivacurium and its 879U84 and 141U86 metabolites:

Urinary excretion of mivacurium and its 879U84 and 141U86 metabolites was virtually complete by 24 hours. Five (5%) percent of the administered dose was excreted as unchanged mivacurium, 36% as 879U84 and 10% as 141U86 and there was no evidence of other metabolites. Of the 5% of unchanged mivacurium excreted in the urine, 0.9% was comprised of *cis-cis*, 1.8% was comprised of *cis-trans*, and 2.4% was comprised of *trans-trans* isomers. Of the 36% of 879U84 excreted in the urine, 13% was comprised of *cis* and 23% was comprised of *trans* isomers.

Plasma concentrations of ^{14}C, mivacurium and its 879U84 and 141U86 metabolites:

Plasma concentration-time profiles for ^{14}C and sum of total mivacurium, 879U84 and 141U86, each expressed in molar mivacurium-equivalents, were virtually superimposable, for both individual patients and mean profiles. This indicates that there was no evidence for plasma metabolites containing the ^{14}C label other than 879U84 and 141U86. The major isomers of the metabolites found in plasma were *cis-* and *trans*-879U84 and *trans*-141U86; *cis*-141U86 concentrations were negligible.

Labeling comments:

The sponsor's following labeling statement on lines 149-152 in the package insert arising from study 12 is acceptable; "The primary elimination pathway for mivacurium is enzymatic hydrolysis by plasma cholinesterase to form the quaternary alcohol and quaternary monester metabolites, both of which are unlikely to produce clinically significant neuromuscular blocking activity".

2.3. HEALTHY SURGICAL PATIENTS

This was an open-label, single center study in eighteen (18) healthy male surgical patients undergoing surgical procedures of low to moderate risk under N_2O/O_2/opioid anesthesia (**Study 29**). After induction of anesthesia, mivacurium was administered as an i.v. infusion at 5 μg/kg/minute for 60 minutes followed by a rate of 10 μg/kg/minute for 60 minutes. The main objective of this study was to determine the pharmaokinetic profile of the individual stereoisomers of mivacurium.

The pharmacokinetic parameters of the two important stereoisomers of mivacurium are listed in Table 1. The two more potent isomers, *trans-trans* (57% of the mixture) and *cis-trans* (36% of the mixture) are extensively metabolized by pChE resulting in very high

clearance values that exceed cardiac output and extremely short (about 2 minutes) terminal half-life values (Table 1). There were no statistically significant differences in steady state clearance (CL_{ss}) or volume of distribution in terminal phase (V_β) values between the 5 µg/kg/minute and 10 µg/kg/minute infusion rates for both *cis-trans* and *trans-trans* isomers indicating that mivacurium exhibits dose-proportionality in the dose range of 5-10 µg/kg/minute. Between the *cis-trans* and *trans-trans* isomers, the CL_{ss} and V_β estimates were twice as high for the *cis-trans* isomer compared to the *trans-trans* isomer. There was a positive correlation between pChE activity and *trans-trans* isomer (r^2=0.33) and pChE activity and the *cis-trans* isomer (r^2=0.32), respectively. In contrast, there was no correlation between pChE activity and the *cis-cis* isomer (r^2=0.016). Because the clearance of the less potent and less abundant (6% of the mixture of the isomers) *cis-cis* isomer is not dependent on pChE activity, its clearance is much lower (4.6 ± 1.1 mL/min/kg) and the terminal half-life is much longer (52.9 ± 19.8 minutes) compared to the *cis-trans* and *trans-trans* isomers.

Table 1. Summary of steady-state pharmacokinetic parameters of mivacurium isomers in healthy surgical patients receiving 5 µg/kg/minute infusion for one hour followed by 10 µg/kg/minute for one hour (mean (%CV)).

Pharmacokinetic Parameter	Infusion Rate (µg/kg/minute)	*trans-trans* Mivacurium	*cis-trans* Mivacurium
CL_{ss}, mL/minute/kg	5 10	59.4 (45) 53.2 (38)	100 (61) 98.7 (46)
V_β, L/kg	5 10	0.16 (37) 0.147 (35)	.0.292 (78) 0.276 (79)
$t_{1/2}$, minute	-	2.0 (35)	1.8 (61)

Labeling Comments

The sponsor's labeling statements on lines 186-188 and 195-210 of the package insert arising out of Study 29 should be modified as follows (note: the *in vitro* results mentioned in the metabolism subsection come from report TBZZ/93/0062 which was discussed in section 2.1 of this review);

Note: Underlined and strikethrough text indicate material to be inserted and deleted, respectively.

3.0. SPECIAL POPULATIONS

3.1. HEPATIC FAILURE

This was an open-label, single center study in twenty-two (22) patients undergoing surgical procedures of short duration under N_2O/O_2/isoflurane anesthesia (**Study 8**). There were 5 patients with mild hepatic dysfunction in Child's group A, 6 patients with moderate hepatic dysfunction in Child's group B, 1 patient with severe hepatic dysfunction in Child's group C and 10 patients with normal hepatic function. After induction of anesthesia with i.v. midazolam together with fentanyl followed by thiopentone, mivacurium was administered as an i.v. infusion at 15 μg/kg/minute for 10 minutes (total dose of 0.15 mg/kg).

Due to slow patient recruitment, only one patient was entered into the severe hepatic failure group. Therefore, comparisons between groups involved the control, mild and moderate hepatic failure groups only. Examination of the pharmacokinetic parameters of the sole patient (number 19) in the severe hepatic failure group did not reveal any dramatic changes compared to patients in the other groups. Values of clearance and terminal half-life for this patient were within the group ranges seen in mild and moderate hepatic failure patient groups.

Tables 2 and 3 show the pharmacokinetic parameters and the pharmacodynamic data, respectively, following the infusion of mivacurium. The onset and depth of neuromuscular block were similar in healthy adults and in patients with with mild or moderate hepatic dysfunction. The recovery profile data showed that recovery times tend to increase with severity of the hepatic impairment. Statistically, there was no difference in the recovery profile in normal

patients and patients with moderate hepatic dysfunction. However, the recovery times showed statistically significant differences in normal patients and patients with moderate dysfunction.

The majority of pharmacokinetic parameters, for the *cis-trans* and *trans-trans* mivacurium isomers, were statistically significantly affected by moderate hepatic dysfunction. There was a high correlation (r^2=0.72 and 0.73, respectively) between pChE activity and total clearance of the *cis-trans* and *trans-trans* isomers. Plasma cholinesterase activity appears to be related to degree of hepatic dysfunction. The clearance of both *cis-trans* and *trans-trans* isomers decreased as a function of hepatic dysfunction. There was about 50% decrease in the clearance in patients with moderate hepatic dysfunction when compared with patients with normal hepatic function. There was about two fold increase in C_{max} for both isomers in patients with moderate hepatic dysfunction. For the *cis-cis* isomer, there were trends for increased $AUC_{0-\infty}$ and $t_{1/2}$ with increasing hepatic dysfunction, however these were not statistically significant between the groups. A plot of pChE activity versus total plasma clearance did not show high correlation (r^2=0.44) indicating that the metabolism of this isomer is less dependent on pChE activity. For the "quaternary monoester" (879U84) and "quaternary alcohol" (141U86) metabolites, C_{max} was decreased slightly in patients with mild and moderate dysfunction due to reduced metabolic clearance of the parent compounds, however, the half-life was longer in these patients due to reduced organ clearance. The effect of these two factors was to reduce the maximum concentration observed but increase the exposure factor by 2 to 2.5.

Labeling Comments

The sponsor's following labeling statements on lines 311-316 of the package insert arising out of study 8 are acceptable;

"A separate study compared the pharmacokinetics and pharmacodynamics of mivacurium in patients with mild or moderate cirrhosis to healthy adults with normal hepatic function (Table 6). Although the number of patients in each group is small, the CL values of the more potent isomers, *trans-trans* and *cis-trans*, are lower in patients with mild or moderate cirrhosis as expected based on the marked decreases in plasma cholinesterase activity in this population (see PREAUTIONS: Reduced Plasma Cholinesterse Activity)."

However, in Table 6 of the package insert on lines 318-324, the half-lives of the *cis-cis* isomer for the different groups should be marked as not available as the values listed as proposed are distribution half-lives and not terminal half-lives unlike for the *cis-trans* and *trans-trans* isomers"

Table 2. Pharmacokinetic parameters of mivacurium isomers in control subjects, and in patients with mild hepatic dysfunction and moderate hepatic dysfunction (mean (%CV)).

Pharmacokinetic Parameter	*cis-trans* mivacurium			*trans-trans* Mivacurium		
	Control	Mild	Moderate	Control	Mild	Moderate
CL, mL/minute/kg	123.6 (45)	73.0 (43)	52.1 (77) *	66.2 (38)	43.1 (38)	30.7 (65) *
$t_{1/2}$, minute	1.2 (42)	1.6 (31)	1.9 (42)	2.4 (42)	3.7 (43)	5.3 (45) *
V_β, mL/kg	200.8 (47)	151.8 (40)	110.7 (33) *	203.6 (25)	221.2 (63)	190.5 (37)

*95% confidence interval indicated a difference between the means of control group and moderate hepatic failure.

Table 3. Pharmacodynamic data following the initiation of infusion of mivacurium in control subjects, and in patients with mild hepatic dysfunction and moderate hepatic dysfunction (mean (%CV)).

Parameter	Control (n=10)	Mild (n=5)	Moderate (n=5)
Maximum block (%)	96.0 (6)	98.6 (1)	97.6 (3)
Time to maximum block (minute)	12.1 (16)	12.4 (16)	13.1 (15)
Time to 25% T_1 recovery (minute)	23.0 (17)	27.8 (24)	32.6 (38)*
Time to 95% T_1 recovery (minute)	38.7 (23)	38.3 (23)	75.0*
Time to T_4:$T_1 \geq 70\%$ (minute)	34.5 (16)	47.4 (29)	53.8 (39)*
25-75% recovery index (minute)	7.3 (21)	9.5 (30)	16.4 (49)*

* 95% confidence interval indicated a difference between the means of control group and moderate hepatic failure.

3.2. RENAL DYSFUNCTION

This was an open-label, single center study in 27 patients undergoing elective surgical procedures of at least 60 minute duration during N_2O/O_2/narcotic anesthesia (**Study 11**). Patients were divided into three groups based on their serum creatinine levels; Group 1- eleven patients with normal renal function (serum creatinine level ≤110 µmol/liter); Group 2- eight patients with mild to moderate renal dysfunction (serum creatinine levels of 150-300 µmol/liter); and Group 3- eight patients with severe renal dysfunction (serum creatinine level of >700 µmol/liter).

There was no significant effect of renal impairment on the pharmacokinetics of the active *cis-trans* and *trans-trans* isomers of mivacurium. This is not unexpected as these isomers are primarily dependent on plasma cholinesterase activity for clearance from the plasma which

was also confirmed by the high correlations of plasma clearance of the active isomers and plasma cholinesterase activity. Pharmacokinetic parameters such as clearance, half-life, and terminal volume of distribution were similar between subjects with normal renal function and patients with mild to moderate and severe renal impairment for both *cis-trans* and *trans-trans* isomers of mivacurium (Table 4).

There were, however, significant differences in the pharmacokinetics of both the inactive *cis-cis* mivacurium and the metabolites. These differences were larger between patients with mild to moderate renal dysfunction and patients with normal renal function than they were between patients with severe renal dysfunction and normal renal function. The reason for this is unclear.

Metabolism of mivacurium isomers produced significant amounts of *cis* and *trans* "quaternary monoester" metabolite and the *trans* "quaternary alcohol" metabolite with very small amounts of *cis* "quaternary alcohol" metabolite. The half-life of these metabolites is significantly longer for both mild and severe renal dysfunction groups compared to the control group.

Table 4. Pharmacokinetic parameters of mivacurium isomers in control subjects, and in patients with mild to moderate renal dysfunction and severe renal dysfunction (mean (%CV)).

Pharmacokinetic Parameter	*cis-trans* mivacurium			*trans-trans* Mivacurium		
	Control	Mild	Severe	Control	Mild	Severe
CL, mL/minute/kg	97.1 (56)	93.3 (16)	109.6 (56)	53.5 (40)	49.3 (12)	52.6 (42)
$t_{1/2}$, minute	2.3 (61)	3.7 (51)	2.6 (50)	2.6 (73)	3.6 (86)	3.2 (25)
V_β, mL/kg	303.4 (80)	473.8 (45)	415.7 (71)	178.5 (75)	243.3 (81)	238.0 (48)

Labeling Comments

The sponsor's following labeling statements on lines 253-316 of the package insert arising out of study 11 are acceptable;

"A second study was conducted in seven patients with mild to moderate renal impairment, eight patients with severe renal dysfunction(not undergoing transplantation), and 11 patients with normal function. This study showed that the pharmacokinetics of the more potent (*cis-trans* and *trans-trans*) isomers were not statistically significantly affected by renal impairment or failure (Table 5). However, the CL of the *cis-cis* isomer was lower and the $t_{1/2}$ values of the *cis-cis* isomer and metabolites were longer in patients with renal impairment or failure than in patients with normal renal function. The second study also showed that there were no differences in the average infusion rate required to produce 89% to 99% T_1 suppression, nor were there any differences in the post-infusion recovery profile among these populations (Table 5).

3.3. ELDERLY

Two studies, Study 14 and Study 33, that examined differences between young adults and elderly were submitted in this submission. Although, Study 14 did not show any differences in the pharmacokinetics between the two age groups, Study 33 did show that in the elderly the clearance of the two potent isomers is reduced compared to that in young adults. The

reason for the different results seen in these two studies is unknown but may simply be a reflection of the idiosyncracies of the study designs.

3.3.1 ELDERLY PATIENTS

This was an open label, single center study in 36 young adult (age 18-40 years) and 35 elderly (age ≥65 years) patients undergoing elective surgical procedures of at least 1 hour duration during N_2O/O_2/narcotic anesthesia (**Study 14**). Fourteen (14) young adult and 15 elderly patients were selected for full pharmacokinetic evaluation. Patients were randomized into four groups in each of the young adult and elderly patient groups. One group in each of the young adult and elderly groups received intial i.v doses of 0.03 mg/kg, 0.04 mg/kg, 0.05 mg/kg, and 0.06 mg/kg mivacurium. When maximum block was achieved following the initial dose, a supplementary i.v. bolus dose of mivacurium was given so that each patient received a total dose of 0.1 mg/kg. Intubation was performed when maximum block had been achieved following the second bolus dose. Following spontaneous recovery of T1 to 5-10% of baseline, a continuous i.v. infusion of mivacurium was commenced at an initial rate of approximately 6 μg/kg/minute and subsequently adjusted to maintain neuromuscular block within the range 91-99% T1 suppression for the remainder of the surgical procedure.

Table 5 shows the pharmacokinetic parameters following the infusion of mivacurium. Mean clearances and volumes of distribution were higher and $t_{1/2}$ longer for the elderly group, but with the exception of V_β for *trans-trans* mivacurium, there were no statistically significant differences between the age groups in any pharmacokinetic parameters of the mivacurium isomers.

Labeling comments:

The sponsor's following labeling statements on lines 236-237 of the package insert arising out of Study 14 are acceptable;

"The study showed no clinically important differences in the pharmacokinetics of individual isomers"

Table 5. Mean (%CV) mivacurium isomer non-compartmental pharmacokinetic parameter estimates in young adults (n=14) and elderly (n=15).

Pharmacokinetic Parameter	*cis-cis* isomer		*cis-trans* isomer		*trans-trans* isomer	
	Young	Adult	Young	Adult	Young	Adult
Cl_{ss}[a], mL/kg/minute			118 (44)	186 (62)	64 (42)	87 (47)
CL[b], mL/kg/minute	4.3 (19)	5.1 (41)	117 (68)	209 (79)	58 (37)	78 (51)
$t_{1/2\beta}$[c], minute	55 (25)	66 (54)	2.6 (58)	3.5 (83)	3.4(74)	4.6 (46)
V_β[f], mL/kg	337 (23)	430 (54)	424 (75)	956 (94)	236 (55)	508 (55)

[a] Clearance at steady state

[b] Total plasma clearance

[c] Terminal phase elimination half-life

[f] Apparent volume of distribution during the terminal phase

3.3.2. ELDERLY PATIENTS RECEIVING LONG TERM INFUSIONS

This was an open-label efficacy, safety, and pharmacokinetic study of mivacurium adminsitered as an initial single i.v. bolus dose (0.15 mg/kg) and subsequently, either short term (1-3 hours) or long term (4-6 hours) maintenance i.v. infusion **(Study 33)**. The study population comprised three major treatment groups: group A (young adults [18-59 years] receiving short-term infusion, n=12); group B1 (young adults [18-59 years] receiving long-term infusion, n=20); and group B2 (elderly patients [60-81 years] receiving long-term infusion, n=19). Comparisons between the young adults patients receiving long term infusions and elderly patients was done to determine if there were any age related differences.

Table 6 displays the steady state clearance values of the more important *cis-trans* and *trans-trans* isomers. The clearance was lower in elderly patients than in young patients for both *cis-trans* and *trans-trans* isomers. Clearance values for *cis-cis* isomer could not be calculated as it has a long terminal half-life (54 minutes) and infusion rates were changed in most patients within 160 minutes before steady state concentrations were achieved.

Labeling claims:

The following labeling claims were made from Study 33 on lines 222-229 of the package insert and the pharmacokinetic aspects of the claims are acceptable;
"The study compared the pharmacokinetics and pharmacodynamics of mivacurium in 19 elderly patients with those in 20 adult patients receiving infusions for as long as 4 to 6 hours. The average infusion rate required to produce 89% to 99% T1 suppression was slightly (~14%) lower in elderly patients. This difference is not regarded as clinically important, but is most likely secondary to differences in pharmacokinetics (i.e. a lower clearance of the *cis-trans* and *trans-trans* isomers in elderly patients) (Table 4). The rate of post-infusion spontaneous recovery was not dependent on duration of infusion and appeared to be comparable in these elderly patients and adult patients"

Table 6. Steady-state clearance values of cis-trans and trans-trans isomers of mivacurium in adult patients (18-58 years) and elderly patients (60-81 years) receiving long-term (4 to 6 hours) infusions .

Parameter	Isomer	Adult Patients (n=12)	Elderly Patients (n=8)
Clearance (mL/min/kg)	*trans-trans*	54 (34-129)	32 (18-55)
	cis-trans	91 (27-825)	47 (24-93)

4.0. PACKAGE INSERT

The changes proposed by this reviewer to the pharmacokinetic section of the package insert are shown in the package insert attached in Appendix II.

APPENDIX I

IN VITRO HYDROLYSIS

Title: *In Vitro* Hydrolysis Of The Stereoisomers Of Mivacurium In Human Plasma.
NDA: 20-098 **Supplement No.:** SLR-009 **Report No.:** TBZZ/93/0062 **Volume**: 1 of 9
Labeling Comments:

The mean ± S.D. *in vitro* $t_{1/2}$ values of the *trans-trans* and the *cis-trans* isomers were 1.3 ± 0.3 and 0.8 ± 0.2 minutes, respectively, in human plasma from healthy male (n=5) and female (n=5) volunteers. The mean *in vivo* $t_{1/2}$ values for the more potent *trans-trans* and *cis-trans* isomers in healthy surgical patients (Table 3) were similar to those found *in vitro*, suggesting that hydrolysis by plasma cholinesterase is the predominant elimination pathway for these isomers. The mean ± S.D. *in vivo* $t_{1/2}$ for the *cis-cis* isomer in healthy surgical patients was 53 ± 20 minutes. These data suggest that *in vivo*, pathways other than hydrolysis by plasma cholinesterase contribute to the elimination of the *cis-cis* isomer.

Discussion:

Data on *in vitro* esterase hydrolysis of mivacurium was submitted to the Agency on March 1, 1994. However, this data was found to be deficient by the reviewing pharmacokineticist on the following two aspects;

(1) Only an internal report was cited *in lieu* of submitting full analytical method validation. Specifically, the reviewer requested results of daily standard curves and representative chromatograms showing discrimination of the isomers.
(2) The composition of mivacurium used in the *in vitro* study comprised of 45.9% of *trans-trans*, 40.6% of *cis-trans*, and 9.5% of *cis-cis* isomers. This works out to be a combined *trans-trans* and *cis-trans* amount of 86.5 or 5.5% below the NDA content specification of % composition of these isomers. The reviewer requested the sponsor to provide a rationale for the use of a sub-standard drug product.

The reviewer further recommended that if the sponsor adequately addressed the above two deficiencies, then the pharmacokinetic section of the current package insert should be revised incorporating this data into the metabolism section.

The sponsor in this submission submitted the results of the standard curves and represantative chromatograms showing discrimination of the three isomers. The submitted analytical data appears to be satisfactory. Since the objective of this study was to determine the relative rates of disappearance of the isomers in plasma *in vitro*, the sponsor chose the batch with highest *cis-cis* isomer concentration (%) as high initial concentrations were needed to allow for adequate characterization of the concentrations for these isomer as a function of time. Further, the sponsor stated that the *in vitro* disappearance rates determined for the isomers would not be affected by the relative differences in the isomer content of the drug product. The rationale provided by the sponsor appears to be reasonable.

The rates of hydrolysis of the *trans-trans*, *cis-trans*, and *cis-cis* isomers of mivacurium were studied *in vitro* in human plasma from five male and five female volunteers (Report TBZZ/93/0062). The pharmacologically active *trans-trans* and *cis-trans* isomers were rapidly hydrolyzed by plasma cholinesterase with mean *in vitro* half-lives of 1.3 ± 0.3, and 0.8 ± 0.2 minutes, respectively. The relatively inactive *cis-cis* isomer disappeared much more slowly with an *in vitro* half-life of 275 ± 130 minutes. No gender differences were seen in the rates of hydrolysis of the stereoisomers. The sponsor compared this *in vitro* data with *in vivo* elimination half-lives of the stereoisomers of mivacurium in healthy surgical patients. The mean elimination

half-lives for the *trans-trans*, *cis-trans*, and *cis-cis* isomers in these patients were 2.0 ± 0.7, 1.8 ± 1.1, and 52.9 ± 19.8 minutes, respectively. These data indicate that the *in vitro* and *in vivo* half-lives determined for the *trans-trans* and *cis-trans* isomers are similar. However, the half-life of the *cis-cis* isomer is longer *in vitro* than *in vivo* suggesting that another route of elimination, other than ester hydrolysis, is important for the *cis-cis* isomer *in vivo*.

MASS BALANCE STUDY

Title: The Disposition Of A Single Intravenous Bolus Dose Of ^{14}C-Mivacron In Healthy Male Patients Undergoing Scheduled Anesthesia.

NDA: 20-098 **Supplement No.:** SLR-009 **Study**: 12 **Volume**: 9 of 9

Investigator

Labeling comments

The primary elimination pathway for mivacurium is enzymatic hydrolysis by plasma cholinesterase to form the quaternary alcohol and quaternary monester metabolites, both of which are unlikely to produce clinically significant neuromuscular blocking activity" is reasonable.

Objectives

To determine the metabolite profile and rates and routes of excretion of ^{14}C-Mivacurium in man following a single i.v. dose of 0.15 mg/kg.

Study Design

This was an open label study with six (6) male patients undergoing elective extraction of wisdom teeth under nitrous oxide/oxygen/isoflurane anesthesia after induction with thiopentone. Venous blood samples were collected just prior to injection, and at 1, 2, 4, 6, 9, 12, 15, 20, 30, 45, 60 and 90 minutes, and at 2, 3, 4, 6, 8, 12, and 24 hours post dose. The amount of radioactivity in all samples of plasma, blood, urine, feces, and the CO_2-absorber used during the anesthetic was determined. Concentrations of the *cis-cis*, *cis-trans*, and *trans-trans* isomers of mivacurium and the cis- and trans- isomers of 879U84 (the monester metabolite) were assayed in plasma and urine, *cis-* and *trans-* 141U86 (the quaternary alcohol) were assayed in plasma, and total 141U86 was assayed in urine.

Results and Discussion

^{14}C Recovery in urine, feces, and breath:

The mean total percentage recovery of ^{14}C in urine and feces was 101% of the ^{14}C dose administered (approximately 40% of the dose in the urine and 60% in the feces). Urinary excretion of ^{14}C was complete by 24 hours. However, the recovery of ^{14}C in feces continued up to 168 hours. Since, all the patients received morphine for pre-medication and some of the patients also received opioids for post-operative analgesia, the prolonged recovery of ^{14}C in the feces when the recovery was complete within 24 hours in the urine may have been caused by the constipating effects of the opioids. No ^{14}C was excreted as $^{14}CO_2$ during the course of the anesthetic.

Urinary excretion of mivacurium, its 879U84 and 141U86 metabolites:

Urinary excretion of mivacurium, its 879U84 and 141U86 metabolites was virtually complete by 24 hours. Five (5%) percent of the administered dose was excreted as unchanged mivacurium, 36% as 879U84 and 10% as 141U86 and there was no evidence of other metabolites. Of the 5% of unchanged mivacurium excreted in the urine, 0.9% was comprised of *cis-cis*, 1.8% was comprised of *cis-trans*, and 2.4% was comprised of *trans-trans* isomers. Of the 36% of 879U84 excreted in the urine, 13% was comprised of *cis* and 23% was comprised of *trans* isomers.

Plasma concentrations of ^{14}C, mivacurium and its 879U84 and 141U86 metabolites:

Plasma concentration-time profiles for ^{14}C and sum of total mivacurium, 879U84 and 141U86, each expressed in molar mivacurium-equivalents, were virtually superimposable, for

both individual patients and mean profiles. This indicates that there was no evidence for plasma metabolites containing the ^{14}C label other than 879U84 and 141U86. The major isomers of the metabolites found in plasma were *cis*- and *trans*-879U84 and *trans*-141U86; *cis*-141U86 concentrations were negligible.

HEALTHY SURGICAL PATIENTS

Title: Pharmacokinetics and pharmacodynamics of the stereoisomers of mivacurium in healthy surgical patients receiving N_2O/O_2/narcotic anesthesia.

NDA: 20-098 **Supplement No.:** SLR-009 **Study No.:** 29 **Volume**: 8 of 9

Clinical Investigator: [redacted]

Labeling Comments

Distribution:The volume of distribution is relatively small, reflecting limited tissue distribution secondary to the polarity and large molecular weight of mivacurium. The protein binding of mivacurium has not been determined due to its rapid hydrolysis by plasma cholinesterase

Metabolism: The mean in vivo $t_{1/2}$ values for the more potent trans-trans and cis-trans isomers in healthy surgical patients were similar to those found in vitro, suggesting that hydrolysis by plasma cholinesterase is the predominant elimination pathway for these isomers. The mean ± S.D. in vitro $t_{1/2}$ of the less potent cis-cis isomer was 276 ± 130 minutes, while the mean ± S.D. in vivo $t_{1/2}$ for the cis-cis isomer in healthy surgical patients was 53 ± 20 minutes. These data suggest that in vivo, pathways other than hydrolysis by plasma cholinesterase contribute to the elimination of the cis-cis isomer.

Elimination: Clearance and Half-life: The CL values of the two more potent isomers, cis-trans and trans-trans, are very high and are dependent on plasma cholinesterase activity. The combination of high CL and low distribution volume results in $t_{1/2}$ values of approximately 2 minutes for the two more potent isomers. The short $t_{1/2}$ and high CL of the more potent isomers are consistent with the short duration of action of mivacron.

The CL of the less potent cis-cis isomer is not dependent on plasma cholinesterase. The mean ± S.D. CL was 4.6 ± 1.1 mL/min/kg and $t_{1/2}$ was 53 ± 20 minutes in the 18 healthy surgical patients whose data are displayed in table 3.

Objectives:

To determine the pharmacokinetic profile of the individual isomers of mivacurium in healthy surgical patients.

Study Design

This was an open-label, single center study in twenty seven (27) healthy male surgical patients undergoing surgical procedures of low to moderate risk under N_2O/O_2/opioid anesthesia. After induction of anesthesia, mivacurium was administered as an i.v. infusion at 5 µg/kg/minute for 60 minutes followed by a rate of 10 µg/kg/minute for 60 minutes.

Venous blood samples were collected during each infusion rate and for 2 to 4 hours after the cessation of the infusion. Blood samples were drawn at 2, 3, 4, 6, 9, 12, 15, 20, 30, 45, and 60 minutes after initiation of 5 µg/kg/minute infusion. Blood samples were drawn at 2, 3, 4, 6, 9, 12, 15, 20, 30, 45, and 60 minutes after initiation of 10 µg/kg/minute infusion. After termination of 10 µg/kg/minute infusion blood samples were drawn at 1, 2, 3, 4, 6, 8, 12, 20, 30, 45, 60, 90, 120, and 240 minutes.

Results And Discussion

The two more potent isomers, *trans-trans* (57% of the mixture) and *cis-trans* (36% of the mixture) are extensively metabolized by pChE resulting in very high clearance values that exceed cardiac ouput and extremely short (about 2 minutes) terminal half-life values (Table 1). There were no statistically significant differences in steady state clearance (CL_{ss}) or volume of

distribution in terminal phase (V_β) values between the 5 µg/kg/minute and 10 µg/kg/minute infusion rates for both *cis-trans* and *trans-trans* isomers indicating that mivacurium exhibits dose-proportionality in the dose range of 5-10 µg/kg/minute. Between the *cis-trans* and *trans-trans* isomers, the CL_{ss} and V_β estimates were twice as high for the *cis-trans* isomer over the *trans-trans*. There was a positive correlation between pChE activity and *trans-trans* isomer (r^2=0.33) and pChE activity and *cis-trans* isomer (r^2=0.32), respectively. In contrast, there was no correlation between pChE activity and the *cis-cis* isomer (r^2=0.016). Because the clearance of the less potent and less abundant (6% of the mixture of the isomers) *cis-cis* isomer is not dependent on pChE activity, its clearance is much lower (4.6 ± 1.1 mL/min/kg) and the terminal half-life is much longer (52.9 ± 19.8 minutes) compared to the *cis-trans* and *trans-trans* isomers.

Table 1. Summary of steady-state pharmacokinetic parameters of mivacurium isomers in healthy surgical patients receiving 5 µg/kg/minute infusion for one hour followed by 10 µg/kg/minute for one hour (mean (%CV)).

Pharmacokinetic Parameter	Infusion Rate (µg/kg/minute)	*trans-trans* Mivacurium	*cis-trans* Mivacurium
CL_{ss}, mL/minute/kg	5 10	59.4 (45) 53.2 (38)	100 (61) 98.7 (46)
V_β, L/kg	5 10	0.16 (37) 0.147 (35)	.0.292 (78) 0.276 (79)
$t_{1/2}$, minute		2.0 (35)	1.8 (61)

HEPATIC FAILURE

Title: A pharmacokinetic and pharmacodynamic study of mivacurium and its metabolites in surgical patients with normal hepatic function or hepatic dysfunction receiving mivacurium during N_2O/O_2/isoflurane anesthesia.

NDA: 20-098 **Supplement No.:** SLR-009 **Study No.:** 8 **Volume**: 2 of 9

Clinical Investigator: (

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Labeling Comments

A separate study compared the pharmacokinetics and pharmacodynamics of mivacurium in patients with mild or moderate cirrhosis to healthy adults with normal hepatic function (Table 6). Although the number of patients in each group is small, the CL values of the more potent isomers, *trans-trans* and *cis-trans*, are lower in patients with mild or moderate cirrhosis as expected based on the marked decreases in plasma cholinesterase activity in this population (see PREAUTIONS: Reduced Plasma Cholinesterse Activity).

Objectives:

To determine the pharmacokinetic profile of the individual isomers and hydrolytic metabolite isomers, the relationship between varying degrees of hepatic dysfunction and duration of muscular block, and to evaluate the relationship between pharmacokinetic profiles of the individual isomers and neuromuscular block.

Study Design

This was an open-label, single center study in 22 patients undergoing surgical procedures of short duration under N_2O/O_2/isoflurane anesthesia. There were 5 patients with mild hepatic dysfunction in Child's group A, 6 patients with moderate hepatic dysfunction in Child's group B, 1 patient with severe hepatic dysfunction in Child's group C and 10 patients with normal hepatic function. After induction of anesthesia with i.v. midazolam together with fentanyl followed by thiopentone, mivacurium was administered as an i.v. infusion at 15 µg/kg/minute for 10 minutes (total dose of 0.15 mg/kg). Maintenance of anesthesia was with 70% nitrous oxide in oxygen plus incremental doses of fentanyl or midazolam as required.

Venous blood samples were drawn at pre-dose, and at 1, 2, 4, 6, 8, 10, 11, 12, 14, 16, 19, 22, 25, 30, 40, 70, 100, 130, and 190 minutes after initiation of mivacurium infusion. Two additional samples at 240 and 300 minutes were to be collected after termination of infusion wherever possible.

Results And Discussion

Due to slow patient recruitment, only one patient was entered into the severe hepatic failure group. Therefore, comparisons between groups involved control, mild and moderate hepatic failure groups only. Examination of the pharmacokinetic parameters of this sole patient (number 19) in the severe hepatic failure group did not reveal any dramatic changes compared to patients in other groups. Values of clearance and terminal half-life for this patient were within the ranges seen in mild and moderate hepatic failure patient groups. Tables 1 and 2 show the pharmacodynamic data and the pharmacokinetic parameters, respectively, following the infusion of mivacurium. The onset and depth of neuromuscular block were similar in healthy adults and in patients with with mild or moderate hepatic dysfunction. The recovery profile data showed that recovery times tend to increase with severity of the hepatic impairment. Statistically, there was no difference in recovery profile in normal patients and patients with moderate hepatic

dysfunction. However, the recovery times showed statistically significant differences in normal patients and patients with moderate dysfunction.

The majority of pharmacokinetic parameters, for the *cis-trans* and *trans-trans* mivacurium isomers, were statistically significantly affected by moderate hepatic dysfunction. There was a high correlation (r^2=0.72 and 0.73, respectively) between pChE activity and total clearance of the *cis-trans* and *trans-trans* isomers. Plasma cholinesterase activity appears to be related to degree of hepatic dysfunction. The clearance of both *cis-trans* and *trans-trans* isomers decreased as a function of hepatic dysfunction. There was about 50% decrease in the clearance in patients with moderate hepatic dysfunction when compared with patients with normal hepatic function. There was about two fold increase in C_{max} for both isomers in patients with moderate hepatic dysfunction. For the *cis-cis* isomer, there were trends for increased $AUC_{0-\infty}$ and $t_{1/2}$ with increasing hepatic dysfunction, however these were not statistically significant between the groups. A plot of pChE activity versus total plasma clearance did not show high correlation (r^2=0.44) indicating that the metabolism of this isomer is less dependent on pChE activity. For the "quaternary monoester" (879U84) and "quaternary alcohol" (141U86) metabolites, C_{max} was decreased slightly in patients with mild and moderate dysfunction due to reduced metabolic clearance of the parent compounds, however, the half-life was longer in these patients due to reduced organ clearance. The effect of these two factors was to reduce the maximum concentration observed but increase the exposure factor of 2 to 2.5.

Table 1. Pharmacodynamic data following the initiation of infusion of mivacurium in control subjects, and in patients with mild hepatic dysfunction and moderate hepatic dysfunction (mean (%CV)).

Parameter	Control (n=10)	Mild (n=5)	Moderate (n=5)
Maximum block (%)	96.0 (6)	98.6 (1)	97.6 (3)
Time to maximum block (minute)	12.1 (16)	12.4 (16)	13.1 (15)
Time to 25% T_1 recovery (minute)	23.0 (17)	27.8 (24)	32.6 (38)*
Time to 95% T_1 recovery (minute)	38.7 (23)	38.3 (23)	75.0*
Time to T_4:$T_1 \geq$ 70% (minute)	34.5 (16)	47.4 (29)	53.8 (39)*
25-75% recovery index (minute)	7.3 (21)	9.5 (30)	16.4 (49)*

* 95% confidence interval indicated a difference between the means of control group and moderate hepatic failure.

Table 2. Pharmacokinetic parameters of mivacurium isomers in control subjects, and in patients with mild hepatic dysfunction and moderate hepatic dysfunction (mean (%CV)).

Pharmacokinetic Parameter	*cis-trans* mivacurium			*trans-trans* Mivacurium		
	Control	Mild	Moderate	Control	Mild	Moderate
C_{max}, ng/mL	70.2 (43)	106.7(40)	184.9 (53)*	175.7 (34)	239.8 (34)	420.8 (60)*
$AUC_{0-\infty}$, ng.hour/mL	9.3 (46)	15.7 (51)	26.8 (61)*	26.3 (39)	40.4 (44)	69.3 (62)*
CL, mL/minute/kg	123.6 (45)	73.0 (43)	52.1 (77)*	66.2 (38)	43.1 (38)	30.7 (65)*
$t_{1/2}$, minute	1.2 (42)	1.6 (31)	1.9 (42)	2.4 (42)	3.7 (43)	5.3 (45)*
V_{β}, mL/kg	200.8 (47)	151.8 (40)	110.7 (33)*	203.6 (25)	221.2 (63)	190.5 (37)

*95% confidence interval indicated a difference between the means of control group and moderate hepatic failure.

RENAL FAILURE

Title: A pharmacokinetic and pharmacodynamic study of mivacurium and its metabolites in surgical patients with normal renal function or renal dysfunction receiving mivacurium during N2O/O2/Narcotic anesthesia.

Investigator: [ ]

NDA:20-098 **Supplement No.**: SLR-009 **Volume**: 4 **Study No.**: 11

Subject Breakdown

	Normal renal function (n=12) (mean & range)	Mild to moderate renal dysfunction (n=7) (mean (range))	Severe renal dysfunction (n=8) (mean (range))
Weight, kg	69.6 & 48-84	62 & 43-72	66.8 & 40-80
Age, years	44.2 & 20-66	30.2 & 16.9-54.6	46 & 28.2-64.2

Labeling Comments

A second study was conducted in seven patients with mild to moderate renal impairment, eight patients with severe renal dysfunction(not undergoing transplantation), and 11 patients with normal function. This study showed that the pharmacokinetics of the more potent (cis-trans and trans-trans) isomers were not statistically significantly affected by renal impairment or failure (Table 5). However, the CL of the cis-cis isomer was lower and the t1/2 values of the cis-cis isomer and metabolites were longer in patients with renal impairment or failure than in patients with normal renal function. The second study also showed that there were no differences in the average infusion rate required to produce 89% to 99% T1 suppression, nor were there any differences in the post-infusion recovery profile among these populations (Table 5).

Objectives:

(1) To evaluate the relationship between varying degrees of renal dysfunction and duration of neuromuscular block in surgical patients.
(2) To determine the pharmacokinetic profile of the individual isomers of mivacurium in these patients.
(3) To determine the pharmacokinetic profile of the hydrolytic metabolite isomers of mivacurium in these patients.
(4) To evaluate the relationship between neuromuscular block and the pharmacokinetic profiles of the individual mivacurium isomers in these patients.

Study design:

This was an open-label, single center study in 27 patients undergoing elctive surgical procedures of at least 60 minute duration during N_2O/O_2/narcotic anesthesia. Patients were divided into three groups based on their serum creatinine levels; Group 1- eleven patients with normal renal function (serum creatinine level ≤110 μmol/liter); Group 2- eight patients with mild to moderate renal dysfunction (serum creatinine levels of 150-300 μmol/liter); and Group 3- eight patients with severe renal dysfunction (serum creatinine level of >700 μmol/liter). Blood was sampled at 0, 1, 2, 5, 10, 11, 12, 15, 20, 30, 45, and 60 minutes after the start of the infusion and then at 30 minute intervals until the infusion was turned off and at 0, 1, 2, 5, 10, 15, 30, 45, 60, 120, 180, 240 and 300 minutes after termination of infusion.

Results And Discussion

There was no significant effect of renal impairment on the pharmacokinetics of the active *cis-trans* and *trans-trans* isomers of mivacurium. This is not unexpected as these isomers are primarily dependent on plasma cholinesterase activity for clearance from the plasma which was also confirmed by the high correlations of plasma clearance of the active isomers and plasma cholinesterase activity. Pharmacokinetic parameters such as clearance, half-life, and terminal volume of distribution were similar between subjects with normal renal function and patients with mild to moderate and severe renal impairment for both *cis-trans* and *trans-trans* isomers of mivacurium (Table 1).

There were, however, significant differences in the pharmacokinetics of both the inactive *cis-cis* mivacurium and the metabolites. These differences were larger between patients with mild to moderate renal dysfunction and patients with normal renal function than they were between patients with severe renal dysfunction and normal renal function. The reason for this is unclear.

Metabolism of mivacurium isomers produced significant amounts of *cis* and *trans* "quaternary monoester" metabolite and the *trans* "quaternary alcohol" metabolite with very small amounts of *cis* "quaternary alcohol" metabolite. The half-life of these metabolites is significantly longer for both mild and severe renal dysfunction groups compared to the control group.

Table 1. Pharmacokinetic parameters of mivacurium isomers in control subjects, and in patients with mild to moderate renal dysfunction and severe renal dysfunction (mean (%CV)).

Pharmacokinetic Parameter	*cis-trans* mivacurium			*trans-trans* Mivacurium		
	Control	Mild	Severe	Control	Mild	Severe
CL, mL/minute/kg	97.1 (56)	93.3 (16)	109.6 (56)	53.5 (40)	49.3 (12)	52.6 (42)
$t_{1/2}$, minute	2.3 (61)	3.7 (51)	2.6 (50)	2.6 (73)	3.6 (86)	3.2 (25)
V_{β}, mL/kg	303.4 (80)	473.8 (45)	415.7 (71)	178.5 (75)	243.3 (81)	238.0 (48)

ELDERLY

Title: A Study to Evaluate the Dose Response Relationship and Pharmacokinetics of Mivacurium Administered by Bolus Dose and Infusion to Adult and Elderly Surgical Patients During N2O/O2/Narcotic Anesthesia.

NDA: 20-098 **Supplement No.**: SLR-009 **Study:** 14 **Volume**: 5 of 9

Clinical Investigator

Labeling Claims:

The study showed no clinically important differences in the pharmacokinetics of the individual isomers nor the ED_{95} determined for 36 young adult patients (18 to 40 years) and 35 elderly patients (>65 years) during opioid/nitrous oxide/oxygen anesthesia. Following infusions for up to 3.5 hours in these patients, the rate of spontaneous recovery was slightly (~2 to 4 minutes, on average slower in the elderly patients than in young adult patients.

Objectives:

To determine the influence of age on the (i) Dose-response relationship of mivacurium (ii) Pharmacokinetic profile of individual and hydrolytic metabolite isomers and (iii) relationship between neuromuscular block and pharmacokinetic profiles of individual mivacurium isomers.

Study Design:

A total of 36 young adult (age 18-40 years) and 35 elderly (age ≥65 years) patients were recruited into the study of which 14 young adult and 15 elderly patients were selected for full pharmacokinetic evaluation. Patients were randomized into four groups in each of the young adult and elderly patient groups. One group in each of the young adult and elderly groups received intial i.v doses of 0.03 mg/kg, 0.04 mg/kg, 0.05 mg/kg, and 0.06 mg/kg mivacurium. When maximum block was achieved following the initial dose, a supplementary i.v. bolus dose of mivacurium was given so that each patient received a total dose of 0.1 mg/kg. Intubation was performed when maximum block had been achieved following the second bolus dose. Following spontaneous recovery of T1 to 5-10% of baseline, a continuous i.v. infusion of mivacurium was commenced at an initial rate of approximately 6 µg/kg/minute and subsequently adjusted to maintain neuromuscular block within the range 91-99% T1 suppression for the remainder of the surgical procedure.

Venous blood samples were collected at pre-dose, and at 1, 2, 5, minutes following the initial bolus dose of mivacurium and pre-dose and at 1, 2, 5, 10, 20 and 30 minutes following the additional bolus dose of mivacurium. Venous samples were also collected immediately prior to and at 1, 2, 5, 10, 15, 20, 30 minutes following commencement of mivacurium infusion then at 30 minute intervals until the infusion was terminated. If the infusion rate was changed blood samples were collected immediately prior to and at 1, 2, 5 minutes following the change in rate. Three samples were also taken at 5 minute intervals before the infusion was terminated. Additional samples were collected immediately prior to and at 1, 2, 5, 10, 15, 30, 45, 60, 120, 180, 240 and 360 minutes after the infusion was terminated.

Results and Discussion

Table 1 shows the pharmacokinetic parameters following the infusion of mivacurium. Mean clearances and volumes of distribution were higher and $t_{1/2}$ longer for the elderly group, but with the exception of V_β for *trans-trans* mivacurium, there were no statistically

significant differences between the age groups in any pharmacokinetic parameters of the mivacurium isomers.

Table 1. Mean (%CV) mivacurium isomer non-compartmental pharmacokinetic parameter estimates in young adults (n=14) and elderly (n=15).

Pharmacokinetic Parameter	*cis-cis* isomer		*cis-trans* isomer		*trans-trans* isomer	
	Young	Adult	Young	Adult	Young	Adult
Cl_{ss}[a], mL/kg/minute	-	-	118 (44)	186 (62)	64 (42)	87 (47)
CL[b], mL/kg/minute	4.3 (19)	5.1 (41)	117 (68)	209 (79)	58 (37)	78 (51)
$t_{1/2\beta}$[c], minute	55 (25)	66 (54)	2.6 (58)	3.5 (83)	3.4(74)	4.6 (46)
V_β[f], mL/kg	337 (23)	430 (54)	424 (75)	956 (94)	236 (55)	508 (55)

[a] Clearance at steady state
[b] Total plasma clearance
[c] Terminal phase elimination half-life
[f] Apparent volume of distribution during the terminal phase

LONG TERM INFUSIONS

Title: Short- and Long-Term Infusions of Mivacron in Adult Surgical Patients During N_2O/O_2/Opioid anesthesia.

NDA: 20-098 **Supplement No.:** SLR-009 **Study No.:** 33 **Volume**: 6 & 7 of 9

Clinical Investigator: [redacted]

Labeling Claims:

The study compared the pharmacokinetics and pharmacodynamics of mivacurium in 19 elderly patients with those in 20 adult patients receiving infusions for as long as 4 to 6 hours. The average infusion rate required to produce 89% to 99% T1 suppression was slightly (~14%) lower in elderly patients. This difference is not regarded as clinically important, but is most likely secondary to differences in pharmacokinetics (i.e. a lower clearance of the cis-trans and trans-trans isomers in elderly patients) (Table 4). The rate of post-infusion spontaneous recovery was not dependent on duration of infusion and appeared to be comparable in these elderly patients and adult patients.

Study Design:

The study population comprised three major treatment groups: group A (young adults [18-59 years] receiving short-term infusion, n=12); group B1 (young adults [18-59 years] receiving long-term infusion, n=20); and group B2 (elderly patients [60-81 years] receiving long-term infusion, n=19). Short-term infusions lasted between 1-3 hours while long term infusions lasted for 4-6 hours. Within these groups, patients were subgrouped for analyses by pChE activity (normal vs. low) and stability of infusion requirements over time (constant vs. decreasing) to describe results for most patients (i.e., patients with stable infusion rates and normal pChE activities) and for subgroups of patients important to the clinician. Blood samples were collected prior to the initial dose of mivacurium, at 30 minute intervals during the infusion and at discontinuation of infusion.

Objectives:

(1) To evaluate the efficacy and safety of mivacurium following short-term (1 to 3 hour) and long-term (4 to 6 hour) infusions, with particular emphasis on the time course of spontaneous recovery following cessation of infusion in young adult and elderly patients.

(2) To determine the plasma concentrations of mivacurium isomers (and major metabolites), with particular emphasis on quantification of the *cis-cis* isomer levels over time and the question of whether accumulation of this isomer may influence the post-infusion recovery profile.

Results and Discussion:

Table 1 displays the steady state clearance values of the more important *cis-trans* and *trans-trans* isomers. The clearance was lower in elderly patients than in young patients for both *cis-trans* and *trans-trans* isomers. Clearance values for *cis-cis* isomer could not be calculated as it has a long terminal half-life (54 minutes) and infusion rates were changed in most patients within 160 minutes before steady state concentrations were achieved.

Table 1. Steady-state clearance values of cis-trans and trans-trans isomers of mivacurium in adult patients (18-58 years) and elderly patients (60-81 years) receiving long-term (4 to 6 hours) infusions .

Parameter	Isomer	Adult Patients (n=12)	Elderly Patients (n=8)
Clearance (mL/min/kg)	*trans-trans*	54 (34-129)	32 (18-55)
	cis-trans	91 (27-825)	47 (24-93)